

Comorbidities and Psoriasis

Joel M. Gelfand, MD, MSCE, FAAD, interviewed by Kari Lyn Martin, MD, FAAD

KARI LYN MARTIN, MD, FAAD: Hello, everybody, welcome to *Dialogues in Dermatology*. I'm excited to have Dr. Joel Gelfand with me today. He is a Professor of Dermatology and Epidemiology at the University of Pennsylvania's Perelman's School of Medicine. He's also the Vice Chair of Clinical Research, Medical Director of the Dermatology Clinical Studies Unit, and Director of the Psoriasis and Phototherapy Treatment Center. He's a nationally and internationally recognized expert in psoriasis, clinical epidemiology, drug safety, and clinical trials.—

--The overarching goal of his research in clinical practice is to improve psoriasis patient outcomes on the skin and joints, while lowering the risk of diabetes, cardiovascular disease, and mortality. And I am Kari Martin, an Associate Professor of Dermatology and Child Health at the University of Missouri in Columbia. And we are so excited to have you, thanks for joining us, Dr. Gelfand.

JOEL M. GELFAND, MD, MSCE, FAAD: Kari, it's great to be back on *Dialogues in Dermatology*, thanks for having me.

KARI LYN MARTIN, MD, FAAD: We're going to be chatting today about comorbidities and psoriasis. And I always love to hear kind of where you started, how you landed down this specific track, what grabbed you about psoriasis and specifically comorbidities?

JOEL M. GELFAND, MD, MSCE, FAAD: It's a great question. Back in medical school and residency, I sort of knew I wanted to do clinical research and got interested in psoriasis early on, because I sort of got interested in complex medical dermatology and psoriasis is obviously one of the more common significant medical illnesses we deal with as dermatologists, it's one of the top ten diagnoses that come into our clinics. And as a person who is interested in epidemiology,

we like to study things that can have a big impact on population health. So there's over 8 to 9 million people with psoriasis in the United States, over 125 million people worldwide.—

--And so that drew me to this field. And then it occurred to me, and this is sort of back in the late '90s, early 2000s, that despite there being a lot of work in psoriasis, there actually was not a lot of work done on just the basic natural history of the disease. It was very few studies done looking at sort of basic population prevalence of the disease, looking longitudinally at the disease over time, and understanding what health issues may be occurring in people with psoriasis, either related to the disease itself, other factors that come along with psoriasis, or the treatments that we use for psoriasis.—

--So it was really sort of a great sort of scientific opportunity to better understand this disease and take these findings, both from the research setting back to the clinic, and from the clinic back to the research setting. And as I think we'll get to talk about, it's been quite a productive journey for me.

KARI LYN MARTIN, MD, FAAD: What are some of the updates in the last few years, maybe five to ten years or so, that we've been learning surrounding comorbidities in psoriatic patients?

JOEL M. GELFAND, MD, MSCE, FAAD: I think the most important updates that our colleagues need to know about is that one, it's pretty firmly established now that people with psoriasis have a higher risk of diabetes and cardiovascular disease, and that often it seems to be independent of traditional risk factors. And it's clinically significant, particularly in those who have more severe psoriasis, people who are candidates for systemic or phototherapy or those who have more than 10 percent of their body surface area involved with psoriasis.—

--So, for example, what we've been doing is a prospective cohort study, called the Incident Health Outcomes and Psoriasis Events Study, or iHOPE. And this is nested in an electronic

medical records system in the United Kingdom. And we've been following people since 2009 and what we've been able to show in recent publications in the JAAD is that simple estimates of the body surface area affected by psoriasis have important prognostic information for the patient.—

--So, for example, for every 10 percent increase in body surface area a person with psoriasis exhibits, there's a corresponding 20 percent higher risk of developing diabetes over time, independent of things like their body mass index. So it's not because they're overweight per se, but something about the severity of their skin disease driving their likelihood of developing diabetes. Similar story with mortality. People who have 10 percent or more body surface area of psoriasis involved have about an 80 percent higher risk of dying over a period of 4 or 5 years follow up, independent of all of the mortality risk factors that are available to the general practitioner in their medical record.—

--That's a pretty powerful finding to think about. These are GPs, untrained, just answering a simple survey for us, for our research setup that we have there, so the response rate is very high, 96 percent response rate. And there are simple categorizations of disease activity have really important prognostic implications for our patients. And when I started my career back in the early 2000s, most people felt like psoriasis was a benign disease and had no impact on health outcomes and certainly had no impact on longevity, and clearly that's been wrong.—

--Now, I think what we've learned in the last four or five years or so is more about sort of mechanism of action, how does psoriasis seem to relate to these shared comorbidities. And some of it is likely shared genetics. There's a number of genetic pathways, the CDKAL1 gene that makes you more prone to developing psoriasis, but also more prone to developing diabetes. We know from Mendelian randomization studies, where there's clearly some type of a causal link between obesity and developing psoriasis.—

--So there's been lots of epidemiological studies showing that being overweight, and almost a dose response mattered, that the higher your BMI is, there's a direct relation between risk of developing psoriasis over time. And there likely must be some genetic driver shared between these two sort of metabolic inflammatory states, if you will. And then we've also learned a lot more at the imaging level. So a colleague of mine, Nehal Mehta, NHLBI, he and I collaborate a lot in this area.—

--He's leading a very large prospective cohort study of people with psoriasis, where he's able to really deeply phenotype these patients, several hundred patients, at the NIH with very specific imaging modalities. And what we've shown and what he's shown is, one, they have higher amounts of aortic vascular inflammation, measured by PET CT scans. We know that this is a marker of future cardiovascular risk and that it correlates with their PASI score. So similar to what I mentioned earlier, more skin involvement, more risk of say diabetes and mortality, also more risk of aortic vascular inflammation measured by imaging.—

--And then they've developed this sort of more advanced methods of looking at coronary disease with sort of high-resolution CT images of the coronary arteries. And they could show that people with psoriasis have both more coronary disease than they should based on their risk factors. But also, the type of coronary disease called noncalcified plaque that is more likely to lead to an event. So not only do they have more coronary disease, they have more of the type of plaque that results in events, which is clinically important obviously.—

--And then finally, they also were able to (s/I use this) more innovative approach, what's called high risk features, where they were able to identify things like a necrotic core or other things, the mottling in the arterial intima, and show again that people with psoriasis, they have higher rates of high risk lesions than you would expect based on their age and sex and other cardiovascular risk factors. So these are all key things that it's critical for everyone to need to be aware of.—

--It's really a key that patients know that they have a higher risk of cardiovascular disease somehow related to their psoriasis and that there's things they should be thinking about for prevention. I'll just close with this sort of final thing. There's two sets of guidelines now out speaking to these issues. One, the 2018 American College of Cardiology, American Heart Association guidelines, as well as the 2019 National Psoriasis Foundation, American Academy of Dermatology guidelines, both of which identify psoriasis as a cardiovascular risk enhancer, warranting earlier screening for additional cardiovascular risk factors, as well as probably more aggressive management of traditional cardiovascular risk factors in people who have more severe disease.

KARI LYN MARTIN, MD, FAAD: So if a dermatologist feels comfortable in their practice and they're doing some of that screening themselves, what would those recommendations be? I guess they can always refer back to their patient's primary care doctor or their cardiologist, if they already have one. But are there recommendations that dermatologists should be doing themselves?

JOEL M. GELFAND, MD, MSCE, FAAD: Yeah, absolutely. So the AAD/NPF guidelines speak to this. And essentially it mirrored national guidelines, was that generally speaking patients should be screened for their blood pressure. They should have their lipids screened every three to five years or so. And should have a screening test for diabetes, usually starting sometime around age 40 to 45, but earlier in the case of people who have risk factors, like people with psoriasis, particularly severe psoriasis. And so these are very easy to do.—

--Actually, I routinely do this in my clinical practice for my patients, for several reasons. Number one is for many of my patients, I'm the only clinician who is seeing them. They think they're otherwise healthy, they haven't seen their primary doctor in a while, or they may not have the

time to go back and see their primary doctor to get these things done. And I'm often ordering labs anyway, because we're thinking about systemic therapies for them.—

--So I'm going to screen them with labs for biologics, it's not so hard to order lipids and a hemoglobin A1C. And the lipids, ideally they're done fasting overnight but they don't necessarily have to be done fasting overnight. If you order a non-fasting lipids, the triglycerides may be elevated and hard to interpret, but the LDL and total cholesterol will still be interpretable. And so usually what I'm doing with my patients is ordering those things. And then if they're abnormal, we use EMR, so I have a stock phrase, and I use the American Heart Association educational tools about heart-healthy diets and exercise.—

--So you will see if you screen people with psoriasis for a hemoglobin A1C for diabetes, many of them will be pre-diabetic. Their A1C will be above 5.7, which is in the pre-diabetic range but maybe not diabetic yet. And here, that's an opportunity to prevent developing diabetes, because we know that regular exercise and dietary changes can lower the risk of future diabetes. And sometimes primary doctors will put people on metformin, if necessary to help prevent the onset of true diabetes for our patients.—

--And of course, blood pressure, I do practice in an academic medical center so we routinely check blood pressure on our patients. And again, you'll see if you do that, we find that many of our patients have undiagnosed hypertension. Or there's a lot of white coat hypertension in our practice. Many of our patients, and it's interesting because we do general dermatology, I don't have hard data to prove this, but my sense is that my patients coming in for a skin check, will have a seborrheic keratosis or a nevus, they don't seem to have as much white coat hypertension as my people with psoriasis do, even though they're coming to the same practice.—

--So there may be something unique going on there. But it's simple enough to tell the patient, "Check in the community. Put your arm in one of those blood pressure cuff machines at the pharmacy. It should be 120/80. If it's higher than that, you should talk to a primary doctor to get this evaluated." Because we know from a variety of lines of research that not only people with psoriasis have a higher rate of cardiovascular disease, they're also less likely to be appropriately screened for cardiovascular risk factors.—

--And when they do have cardiovascular risk factors, they tend to be undertreated. And so we think that we could narrow some of this mortality gap just by doing what we know works, which is having their primary doctors treat their hypertension, treat diabetes early, manage cholesterol, if necessary.

KARI LYN MARTIN, MD, FAAD: Do we know much data yet, or maybe what you see in your clinical practice, if there's a correlation between how aggressive we are in treating psoriasis or getting the inflammatory cascade under control and if we can help reduce any of those risk factors? Do we know that yet?

JOEL M. GELFAND, MD, MSCE, FAAD: So this is an area of intense investigation and interest in the field of dermatology, as well as rheumatology and cardiovascular disease. There's been a number of approaches to this topic. So one has been doing the observational studies, where you look at what therapies people are on and see if it relates to reduction in cardiovascular risk over time. And there, therapies like methotrexate and TNF inhibitors seem to be associated with a lower risk of cardiovascular disease over time in people with psoriasis compared to people treated with other therapies.—

--Now, whether that's truly a causal relationship, we don't really know. And there's a pretty strong healthy user effect, meaning that people who get systemic treatment for psoriasis generally speaking are looking after their health pretty well, relative to those who have

significant psoriasis and aren't getting systemic agents. So it's really hard to know if we're looking at a treatment benefit or some other factor that's going on. Then we and some others have done a series of randomized placebo-controlled trials, short term over a period of 12 to 16 weeks, looking at blood-based biomarkers of cardiovascular risk and imaging-based biomarkers of vascular risk.—

--And to summarize briefly, what we've shown is that of things like TNF inhibitors, phototherapy, IL-17 inhibitors, and IL-12/23 inhibitors like ustekinumab, we found that only ustekinumab interestingly improves aortic vascular inflammation at week 12 compared to placebo. We didn't find that for the other treatment modalities. And then for cardio metabolic biomarkers, we found that the most potent antiinflammatory effects that related to cardiovascular disease were seen for TNF inhibitors, and fascinatingly phototherapy.—

--Phototherapy lowered C-reactive protein, as well as interleukin-6, which is known to be causally related to cardiovascular disease. And so it's certainly possible that ultraviolet light may have some benefits on cardiovascular disease, we just don't know for certain based on the current state of the data. And then when it comes to improving insulin resistance, we talk a lot about diabetes. None of our treatments seem to improve insulin resistance, which is quite disappointing and is an area we need to understand better.—

--And only phototherapy interestingly improved lipid metabolism. Their HDL-P, or particle size, improves and we don't understand how that occurs but it's a pretty provocative finding.

KARI LYN MARTIN, MD, FAAD: As a pediatric dermatologist, I've got to ask, I know about the basics of screening also recommended for pediatric patients with psoriasis. Anything else kind of specifically different that's showing up in the data between kids and adults with psoriasis in these comorbidities?

JOEL M. GELFAND, MD, MSCE, FAAD: You know what's pretty striking about kids is that you see the culmination of cardiovascular risk factors starting early. I mean, kids generally speaking are healthy, have very low incidences of cardiovascular risk factors to begin with. And so you would think it would be pretty hard to pick up a signal in a young, otherwise healthy population. But, in fact, there's plenty of data that they suffer from dyslipidemia and diabetes, even type 2, as well as obesity and other metabolic problems at a young age.—

--And so this is an opportunity for children with psoriasis to start introducing concepts of healthy lifestyle, starting to work on these diet and regular exercise. Because the longer people are exposed to cardiovascular risk factors, the larger problem they have long term. So recently a paper came out in one of the major medical journals showing that adolescent onset type 2 diabetes is associated with a higher risk of cardiovascular events within two decades. I mean, these are people in their teens having events in their 30s, which is previously unheard of.—

--And so it's really important for those looking after children with psoriasis, not to be alarmist of course, these kids are healthy and their risk of having an event is close to zero in the next 10, 20 years. But when you think about this more in terms of sort of lifetime cardiovascular risk and a lot of times for people, it's motivating to say, "Okay, yeah, I see this on my skin and now this motivates me to take better care of my health." Whereas other risk factors, like people don't feel any worse if their cholesterol is elevated, blood pressure could be elevated with no symptoms, the same with diabetes, the skin can often be a motivating factor for people, and we should take advantage of that when we counsel our patients.

KARI LYN MARTIN, MD, FAAD: This has been quite informative for me. There's a lot going on and you have a lot of work that you've done, but it sounds like so much left to do, and lots of exciting things going on in the field. What are just a couple of key takeaway points that you'd want our listeners to remember?

JOEL M. GELFAND, MD, MSCE, FAAD: I think the number one key takeaway point is educating our patients with psoriatic disease about the higher risk of developing cardiovascular problems and diabetes, so they're always alerted to the need to have this looked after by someone. And two, I really encourage my colleagues to institute their own traditional cardiovascular risk factor screening. It's easy to do a blood pressure, screen them for hemoglobin A1C, and check for lipids. And I find it's really gratifying personally.—

--Patients often will say, "Well, you're the first doctor to do this for me," and they really appreciate it. And these are patients that we will take care of for many years, decades in many cases. And it's really an opportunity to really help them achieve better outcomes, not just in their skin but in their overall health.

KARI LYN MARTIN, MD, FAAD: Absolutely. It's an area we can make a big difference, if we just kind of know what we're looking for and how to do it, and take the time. Well, thank you so much for joining us on *Dialogues* today. It was great to talk with you about these comorbidities and psoriasis and taking the best care we can of our psoriatic patients. This is Dr. Kari Martin with the University of Missouri, interviewing Dr. Joel Gelfand again from the University of Pennsylvania's Perelman's School of Medicine. Thanks so much for joining us.

Commentary

Abigale Clark and Andrew Desrosiers, MD with Todd Schlesinger, MD, FAAD (ed.)

Psoriasis is a chronic inflammatory skin disease driven by derangements in both the innate and adaptive immune system. It has been recognized that the inflammatory mediators involved in the pathogenesis of psoriasis promote a state of systemic inflammation that goes beyond the skin. Recognizing the presence of systemic inflammation in patients with psoriasis is crucial to understanding the common comorbidities of the disease, as well as how to appropriately manage and care for these patients. In this episode of Dialogues in Dermatology, Dr. Joel M. Gelfand and Dr. Kari Lyn Martin discuss the comorbidities associated with psoriasis and the implications that this information has on proper clinical management.

The pathogenesis of psoriasis is marked by abnormal activity of inflammatory cytokines, including IL-17, IL-23, and tumor necrosis factor (TNF). TNF acts synergistically with IL-17 to upregulate the pro-inflammatory genes in keratinocytes, leading to the abnormal proliferation of keratinocytes seen clinically in plaque psoriasis. TNF and other inflammatory cytokines involved in psoriasis have shown to promote a chronic state of inflammation contributing to cardiovascular disease and metabolic disorders such as type 2 diabetes.¹ In recent years, psoriasis, and particularly severe psoriasis, has been recognized as an independent risk factor for myocardial infarction, stroke, and major adverse cardiac events. Epidemiological studies have demonstrated that psoriasis is associated with increased overall mortality,^{1,2} making appropriate clinical management and patient education a crucial component of improving patient outcomes. In this podcast, Dr. Gelfand dives into the latest research and explains how to implement simple screening protocols and patient education to lower the risk of diabetes, cardiovascular disease, and mortality in patients with psoriasis. Dr. Gelfand underlines the significance of this topic on population health, highlighting that there are currently 8 to 9 million people with psoriasis in the United States and over 125 million worldwide.²

According to Dr. Gelfand, the increased risk of cardiovascular disease and diabetes in patients with psoriasis is both clinically significant and firmly established, particularly in patients requiring phototherapy and those with more than 10 percent of body surface involvement. Dr. Gelfand describes a prospective cohort study called Incident Health Outcomes and Psoriasis Events (iHOPE), nested in an EMR system in the UK, which has been following patients since 2009. This study has shown that estimates of body surface area involvement in patients with psoriasis has important prognostic value for the patient. For example, every 10 percent increase in body surface area involvement has shown to increase the risk of developing diabetes by 20 percent, regardless of other factors such as body mass index. The iHOPE study has shown similar outcomes in the overall risk of mortality, with > 10% body surface involvement associated with an eighty percent increased risk of dying over a 4-to-5-year follow-up period.³

Dr. Gelfand reflects on his early career, stating that in the early 2000s, “most people felt like psoriasis was a benign disease and had no impact on health outcomes and certainly had no impact on longevity, but clearly, that’s been wrong.” Imaging with FDG positron emission tomography/computed tomography has shown that psoriasis has detrimental effects on vascular inflammation and has suggested that the cumulative duration of disease correlates positively with the risk of major adverse cardiovascular events.^{1,2} In a population-based study published by Egeberg *et al.*, there was an additional one percent risk of major adverse cardiac events per additional year of psoriasis duration.⁴

Dr. Gelfand emphasizes the importance of educating patients with psoriasis on their increased risk of cardiovascular disease so that they can start thinking about prevention. Dr. Gelfand also refers to the AAD/NPF guidelines that recommend patients be screened for their blood pressure

and have their lipids screened every three to five years, as well as earlier screening for diabetes in those who have risk factors such as psoriasis.⁵ Dr. Gelfand regularly performs these screenings on his patients and notes that it is easy to order lipids and hemoglobin A1C in addition to the routine labs he orders for biologic therapies. He also comments on the simplicity of using the American Heart Association education tools about heart-healthy diets and exercise if these labs return elevated. Dr. Gelfand states that he has found it very personally gratifying to know that he is helping these patients achieve better outcomes, not just in their skin but in their overall health.

Dr. Martin questions whether aggressive treatment to get the inflammatory cascade under control can help reduce the cardiovascular and metabolic risk factors associated with psoriasis, and Dr. Gelfand explains that this is currently a topic under intense investigation. According to Dr. Gelfand, therapies like methotrexate and TNF inhibitors seem to be associated with a lower risk of cardiovascular disease in patients with psoriasis, but whether it is a true causal relationship remains unknown. Dr. Gelfand does mention that for cardiometabolic biomarkers, his research has found the most potent anti-inflammatory effects related to cardiovascular disease in TNF inhibitors and phototherapy. Interestingly, he explains that phototherapy has shown to lower levels of not only C-reactive protein and IL-6, but also HDL-P (lipid particle size), which significantly contributes to the development of cardiovascular disease.

Dr. Martin, as a pediatric dermatologist, inquires about the impact this information has on pediatric patients with psoriasis. Dr. Gelfand explains that unfortunately, in children with psoriasis, cardiovascular risk factors start early. He adds that these patients may suffer from dyslipidemia, type 2 diabetes, and other metabolic problems at a young age. According to one source, the decrease in longevity in patients with psoriasis starting before age 25 may be as much as 20 years.⁶ Dr. Gelfand explains that this is a great opportunity to introduce the concepts of a healthy lifestyle, diet, and exercise early in children with psoriasis.

Dr. Gelfand makes a key point when he mentions that the skin can be a motivating factor for people, explaining that patients are often motivated to take better care of their health after seeing improvements in their skin. He recommends that we take advantage of this when counseling our patients. Dr. Gelfand emphasizes the importance of educating patients with psoriasis about their higher risk of developing cardiovascular disease and diabetes, so that they're aware and can have this monitored. Lastly, Dr. Gelfand encourages dermatologists to implement cardiovascular risk factor screening methods such as checking blood pressure, hemoglobin A1C, and lipids into their own practices.

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